9/918,039

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	4303	((514/300) or (514/311) or (514/315) or (514/428) or (514/426)).CCLS.	US-PGPUB; USPAT	OR	OFF	2005/12/11 11:11
L2	290	L1 and (thieno or pyrrolo)	US-PGPUB; USPAT	OR	OFF	2005/12/11 11:14

09/ 918,039

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssspta1202txn

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	SEP 09	ACD predicted properties enhanced in REGISTRY/ZREGISTRY
NEWS	4	OCT 03	MATHDI removed from STN
NEWS	5	OCT 04	CA/CAplus-Canadian Intellectual Property Office (CIPO) added to core patent offices
NEWS	6	OCT 13	New CAS Information Use Policies Effective October 17, 2005
NEWS	7	OCT 17	STN(R) AnaVist(TM), Version 1.01, allows the export/download of CAplus documents for use in third-party analysis and visualization tools
NEWS	8	OCT 27	Free KWIC format extended in full-text databases
NEWS	9	OCT 27	DIOGENES content streamlined
NEWS	10	OCT 27	EPFULL enhanced with additional content
NEWS	11	NOV 14	CA/CAplus - Expanded coverage of German academic research
NEWS	12	NOV 30	REGISTRY/ZREGISTRY on STN(R) enhanced with experimental spectral property data
NEWS	13	DEC 05	CASREACT(R) - Over 10 million reactions available

NEWS EXPRESS	DECEMBER 02 CURRENT VERSION FOR WINDOWS IS V8.01, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 02 DECEMBER 2005. V8.0 USERS CAN OBTAIN THE UPGRADE TO V8.01 AT http://download.cas.org/express/v8.0-Discover/
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 10:54:52 ON 11 DEC 2005

=> file reg
COST IN U.S. DOLLARS SINCE FILE TOTAL

	ENTRY	SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 10:55:39 ON 11 DEC 2005

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 9 DEC 2005 HIGHEST RN 869698-41-9
DICTIONARY FILE UPDATES: 9 DEC 2005 HIGHEST RN 869698-41-9

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

```
**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                    *
**********************************************************************
```

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

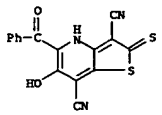
http://www.cas.org/ONLINE/UG/regprops.html

```
=> s "thieno[3,2-b]pyridine"
        208927 "THIENO"
         54512 "3,2-B"
        784693 "PYRIDINE"
L1        1913 "THIENO[3,2-B]PYRIDINE"
                 ("THIENO"(W)"3,2-B"(W)"PYRIDINE")

=> d scan l1
```

09/ 918,039

L1 1913 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN Thieno[3,2-b]pyridine-3,7-dicarbonitrile, 5-benzoyl-2,4-dihydro-6-hydroxy-2-thioxo- (9CI)
MF C16 H7 N3 O2 S2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

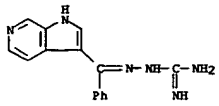
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

09/ 918,039

```
=> s "pyrrolo[2,3-c]pyridin"
         249264 "PYRROLO"
          73810 "2,3-C"
        1145400 "PYRIDIN"
L2         1312 "PYRROLO[2,3-C]PYRIDIN"
                  ("PYRROLO"(W)"2,3-C"(W)"PYRIDIN")

=> d scan l2
```

L2 1312 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN Hydrazinecarboximidamide, 2-(phenyl-1H-pyrrolo[2,3-c]pyridin-3-ylmethylene)- (9CI)
MF C15 H14 N6
CI COM



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

09/ 918,039

```
=> s l1 and l2
L3            5 L1 AND L2

=> file hcaplus
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      28.46      28.67

FILE 'HCAPLUS' ENTERED AT 10:57:01 ON 11 DEC 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 11 Dec 2005  VOL 143 ISS 25
FILE LAST UPDATED: 9 Dec 2005  (20051209/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d l3
YOU HAVE REQUESTED DATA FROM FILE 'REGISTRY' - CONTINUE? (Y)/N:0
YOU HAVE REQUESTED DATA FROM FILE 'REGISTRY' - CONTINUE? (Y)/N:n


=> d his

     (FILE 'HOME' ENTERED AT 10:54:52 ON 11 DEC 2005)

     FILE 'REGISTRY' ENTERED AT 10:55:39 ON 11 DEC 2005
L1          1913 S "THIENO[3,2-B]PYRIDINE"
L2          1312 S "PYRROLO[2,3-C]PYRIDIN"
L3             5 S L1 AND L2

     FILE 'HCAPLUS' ENTERED AT 10:57:01 ON 11 DEC 2005

=> s l3
L4            9 L3

=> d l4 1- ibib abs hitstr
YOU HAVE REQUESTED DATA FROM 9 ANSWERS - CONTINUE? Y/(N):y
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L4 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:511199 HCAPLUS
DOCUMENT NUMBER: 143:145801
TITLE: Ligand-based assessment of factor Xa binding site flexibility via elaborate pharmacophore exploration and genetic algorithm-based QSAR modeling
AUTHOR(S): Taha, Mutasem O.; Qandil, Amjad M.; Zaki, Dhia D.; AlDamen, Murad A.
CORPORATE SOURCE: Faculty of Pharmacy, Department of Pharmaceutical Sciences, University of Jordan, Amman, Jordan
SOURCE: European Journal of Medicinal Chemistry (2005), 40(7), 701-727
CODEN: EJMCA5; ISSN: 0223-5234
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

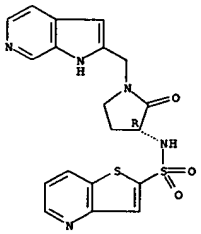
AB The flexibility of activated factor X (fXa) binding site was assessed employing ligand-based pharmacophore modeling combined with genetic algorithm (GA)-based QSAR modeling. Four training subsets of wide structural diversity were selected from a total of 199 direct fXa inhibitors and were employed to generate different fXa pharmacophoric hypotheses using CATALYST software over two subsequent stages. In the first stage, high quality binding models (hypotheses) were identified. However, in the second stage, these models were refined by applying variable feature weight anal. to assess the relative significance of their features in the ligand-target affinity. The binding models were validated according to their coverage (capacity as a three-dimensional (3D) database search queries) and predictive potential as three-dimensional quant. structure-activity relationship (3D-QSAR) models. Subsequently, GA and multiple linear regression (MLR) anal. were employed to construct different QSAR models from high quality pharmacophores and explore the statistical significance of combination models in explaining bioactivity variations across 199 fXa inhibitors. Three orthogonal pharmacophoric models emerged in the optimal QSAR equation suggesting they represent three binding modes accessible to ligands in the binding pocket within fXa.

IT **251938-45-1**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ligand-based assessment of factor Xa binding site flexibility via elaborate pharmacophore exploration and genetic algorithm-based QSAR modeling)

RN 251938-45-1 HCAPLUS
CN Thieno[3,2-b]pyridine-2-sulfonamide, N-[(3R)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

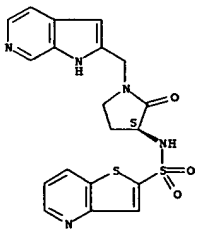
ACCESSION NUMBER: 2004:832890 HCAPLUS
DOCUMENT NUMBER: 142:19473
TITLE: Comparing Ligand Interactions with Multiple Receptors via Serial Docking
AUTHOR(S): Fernandes, Miguel X.; Kairys, Visvaldas; Gilson, Michael K.
CORPORATE SOURCE: Center for Advanced Research in Biotechnology, U. Maryland Biotechnology Institute, Rockville, MD, 20850, USA
SOURCE: Journal of Chemical Information and Computer Sciences (2004), 44(6), 1961-1970
CODEN: JCISD8; ISSN: 0095-2338
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Standard uses of ligand-receptor docking typically focus on the association of candidate ligands with a single targeted receptor, but actual applications increasingly require comparisons across multiple receptors. This study demonstrates that comparative docking to multiple receptors can help to select homol. models for virtual compound screening and to discover ligands that bind to one set of receptors but not to another, potentially similar, set. A serial docking algorithm is furthermore described that reduces the computational costs of such calcns. by testing compds. against a series of receptor structures and discarding a compound as soon as it fails to satisfy specified bind/no bind criteria for each receptor. The algorithm also realizes substantial efficiencies by taking advantage of the fact that a ligand typically binds in similar conformations to similar receptors. Thus, once detailed docking has been used to fit a ligand into the first of a series of similar receptors, much less extensive calcns. can be used for the remaining structures.

IT **209285-84-7**, RPR 208707
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(ligand interactions with multiple receptors via serial docking through electrostatic force and van der Waals forces)

RN 209285-84-7 HCAPLUS
CN Thieno[3,2-b]pyridine-2-sulfonamide, N-[(3S)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:894400 HCAPLUS
DOCUMENT NUMBER: 138:133092
TITLE: Crystal Structures of Two Potent Nonamidine Inhibitors Bound to Factor Xa
AUTHOR(S): Adler, Marc; Kochanny, Monica J.; Ye, Bin; Rumennik, Galina; Light, David R.; Biancalana, Sara; Whitlow, Marc
CORPORATE SOURCE: Berlex Biosciences, Richmond, CA, 94804-0099, USA
SOURCE: Biochemistry (2002), 41(52), 15514-15523
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

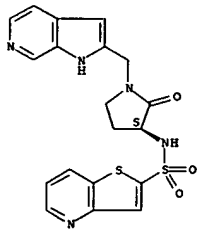
AB There has been intense interest in the development of factor Xa inhibitors for the treatment of thrombotic diseases. Our laboratory has developed a series of novel non-amidine inhibitors of factor Xa. This paper presents two crystal structures of compds. from this series bound to factor Xa. The first structure is derived from the complex formed between factor Xa and compound 1. Compound 1 was the first non-amidine factor Xa inhibitor from our laboratory that had measurable potency in an in vitro assay of anticoagulant activity. The second compound, 2, has a molar affinity for factor Xa (Kiapp) of 7 pM and good bioavailability. The two inhibitors bind in an L-shaped conformation with a chloroarom. ring buried deeply in the S1 pocket. The opposite end of these compds. contains a basic substituent that extends into the S4 binding site. A chlorinated Ph ring bridges the substituents in the S1 and S4 pockets via amide linkers. The overall conformation is similar to the previously published structures for amidine-based inhibitors complexed with factor Xa. However, there are significant differences in the interactions between the inhibitor and the protein at the atomic level. Most notably, there is no group that forms a salt bridge with the carboxylic acid at the base of the S1 pocket (Asp189). Each inhibitor forms only one well-defined hydrogen bond to the protein. There are no direct charge-charge interactions. The results indicate that electrostatic interactions play a secondary role in the binding of these potent inhibitors.

IT **209285-84-7**, RPR-208707
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(structure-activity relationship of factor Xa inhibitors; crystal structures of two potent nonamidine inhibitors bound to factor Xa)

RN 209285-84-7 HCAPLUS
CN Thieno[3,2-b]pyridine-2-sulfonamide, N-[(3S)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

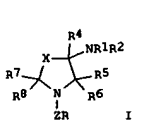
ACCESSION NUMBER: 2001:630893 HCAPLUS
DOCUMENT NUMBER: 135:195505
TITLE: Preparation of azaheterocyclic sulfonamides as factor Xa inhibitors
INVENTOR(S): Choi-Sledeski, Yong Mi; Pauls, Heinz W.; Barton, Jeffrey N.; Ewing, William R.; Green, Daniel M.; Becker, Michael R.; Gong, Yong; Lovell, Julian
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: U.S., 96 pp., Cont.-in-part of U.S. Ser. No. 90,492.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6281227	B1	20010828	US 1999-453307	19991202
WO 9825611	A1	19980618	WO 1997-US22406	19971203
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6602864	B1	20030805	US 1998-90492	19980603
WO 9962904	A1	19991209	WO 1999-US12312	19990603
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
WO 2001039759	A2	20010607	WO 2000-EP11577	20001121
WO 2001039759	A3	20020117		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002013310	A1	20020131	US 2001-918039	20010730

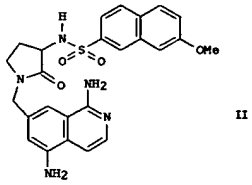
PRIORITY APPLN. INFO.:
US 1996-33159P P 19961213
WO 1997-US22406 A2 19971203
US 1998-90492 A2 19980603
WO 1999-US12312 A2 19990603
US 1999-453307 A 19991202

OTHER SOURCE(S): MARPAT 135:195505
GI

L4 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



I



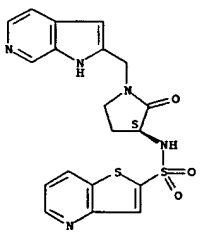
II

AB Title compds. [I; X = (CHR3)m; R = (un)substituted heteroaryl; R1, R2 = H, (un)substituted alkyl, alkenyl, aralkyl; R3 = H, OH, (un)substituted alkyl, aryl, heteroaryl; R4 = H, (un)substituted alkyl, aryl, aralkyl; R5, R6 = H; R5R6 = O; R7, R8 = H, (un)substituted alkyl, aryl, aralkyl, heteroaryl; R7R8 = O; R3R7 = alkylene; m = 0-3] were prepared Thus, title compound II was prepared from 3-acetamido-4-methylbenzaldehyde, malonic acid, and 7-methoxy-2-naphthalenesulfonyl chloride in 10 steps. II had a Ki of 80 nM for inhibition of factor Xa.

IT **209285-84-7P 209285-85-8P 251937-98-1P 251938-46-2P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of azaheterocyclic sulfonamides as inhibitors of factor Xa)

RN 209285-84-7 HCAPLUS
CN Thieno[3,2-b]pyridine-2-sulfonamide, N-[(3S)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



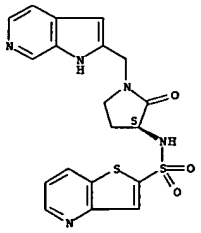
RN 209285-85-8 HCAPLUS
CN Thieno[3,2-b]pyridine-2-sulfonamide, N-[(3S)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]-, bis(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

L4 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

CRN 209285-84-7
CMF C19 H17 N5 O3 S2

Absolute stereochemistry.



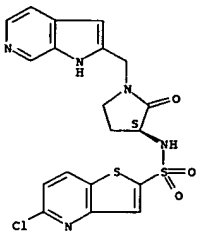
CM 2

CRN 76-05-1
CMF C2 H F3 O2

RN 251937-98-1 HCAPLUS
CN Thieno[3,2-b]pyridine-2-sulfonamide, 5-chloro-N-[(3S)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

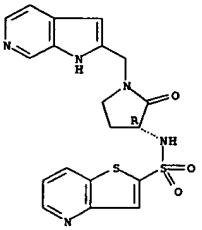


RN 251938-46-2 HCAPLUS
CN Thieno[3,2-b]pyridine-2-sulfonamide, N-[(3R)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]-, bis(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

CRN 251938-45-1
CMF C19 H17 N5 O3 S2

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

L4 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:543073 HCAPLUS
DOCUMENT NUMBER: 133:261091
TITLE: Crystal Structures of Human Factor Xa Complexed with Potent Inhibitors
AUTHOR(S): Maignan, Sebastien; Guilloteau, Jean-Pierre; Pouzieux, Stephanie; Choi-Sledeski, Yong Mi; Becker, Michael R.; Klein, Scott I.; Ewing, William R.; Pauls, Henry W.; Spada, Alfred P.; Mikol, Vincent
CORPORATE SOURCE: Department of Structural Biology, Aventis Pharma, Vitry/Seine, F-94403, Fr.
SOURCE: Journal of Medicinal Chemistry (2000), 43(17), 3226-3232
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

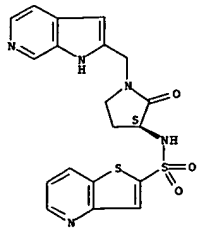
AB Involved in the coagulation cascade, factor Xa (FXa) is a serine protease which has received great interest as a potential target for the development of new antithrombotics. Although there is a great wealth of structural data on thrombin complexes, few structures of ligand/FXa complexes have been reported, presumably because of the difficulty in growing crystals. Reproducible crystallization conditions for human des-Gla1-45 coagulation FXa have been found. This has led to an improvement in the diffraction quality of the crystals (about 2.1 Å) when compared to the previously reported forms (2.3-2.8 Å) thus providing a suitable platform for a structure-based drug design approach. A series of crystal structures of noncovalent inhibitors complexed with FXa have been determined, three of which are presented herein. These include compds. containing the benzamidine moiety and surrogates of the basic group. The benzamidine-containing compound binds in a canonical fashion typical of synthetic serine protease inhibitors. On the contrary, mols. that contain surrogates of the benzamidine group do not make direct hydrogen-bonding interactions with the carboxylate of Asp189 at the bottom of the S1 pocket. The structural data provide a likely explanation for the specificity of these inhibitors and a great aid in the design of bioavailable potent FXa inhibitors.

IT 209285-84-7, RPR 208707
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(crystal structures of human factor Xa complexed with potent inhibitors)

RN 209285-84-7 HCAPLUS
CN Thieno[3,2-b]pyridine-2-sulfonamide, N-[(3S)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

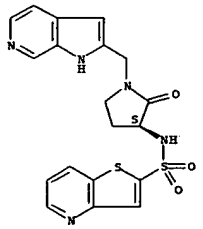
Absolute stereochemistry.

L4 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



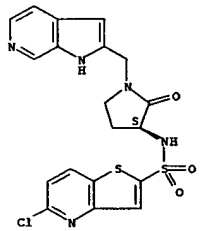
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



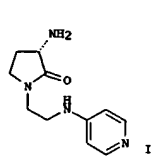
RN 251937-98-1 HCAPLUS
CN Thieno[3,2-b]pyridine-2-sulfonamide, 5-chloro-N-[(3S)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

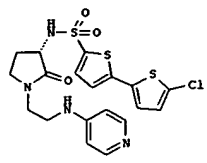


REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:379659 HCAPLUS
DOCUMENT NUMBER: 133:144473
TITLE: Solid-phase parallel synthesis of azarene pyrrolidinones as factor Xa inhibitors
AUTHOR(S): Gong, Yong; Becker, Michael; Choi-Sledeski, Yong Mi; Davis, Roderick S.; Salvino, Joseph M.; Chu, Valeria; Brown, Karen D.; Pauls, Henry W.
CORPORATE SOURCE: Department of Medicinal Chemistry, Rhone-Poulenc Rorer, Collegeville, PA, 19426, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2000), 10(10), 1033-1036
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 133:144473
GI



I



II

AB A focused library (4+14) prepared from 4-aminopyridine and 4-, 5-, and 6-azoindole templates was synthesized using 14 polymer-supported 4-amido-2,3,5,6-tetrafluorophenyl (TFP) sulfonate esters and heteroarylmethyl-substituted arylsulfonylamino pyrrolidinones such as I to give a library of factor Xa inhibitors such as II. Several compds. were identified as factor Xa inhibitors (IC50≤0.1 μM) helping to establish the SAR among these four series of azarene pyrrolidinones. E.g., factor Xa was inhibited by II with a Ki of 15 nM.

IT **209285-84-7P 251937-98-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(solid-phase preparation of a library of heteroarylmethyl arylsulfonylamino pyrrolidinones as factor Xa inhibitors)

RN 209285-84-7 HCAPLUS
CN Thieno[3,2-b]pyridine-2-sulfonamide, N-[(3S)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

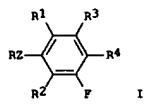
Absolute stereochemistry.

L4 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:819359 HCAPLUS
DOCUMENT NUMBER: 132:64065
TITLE: Preparation of fluorobenzoylated resins as solid phase synthesis supports
INVENTOR(S): Salvino, Joseph M.; Gronsberg, Robert D.; Airey, John E.; Poli, Gregory B.; McGeehan, Gerard M.; Labaudiniere, Richard F.; Clerc, Francois-frederic; Bezard, Daniel Noel Andre
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 113 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9967228	A1	19991229	WO 1999-US14252	19990623
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2335760	AA	19991229	CA 1999-2335760	19990623
AU 9947128	A1	20000110	AU 1999-47128	19990623
AU 764153	B2	20030814		
BR 9911487	A	20010320	BR 1999-11487	19990623
EP 1089988	A1	20010411	EP 1999-930628	19990623
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO				
JP 2002518555	T2	20020625	JP 2000-555882	19990623
US 6639023	B1	20031028	US 2000-487950	20000119
NO 2000006662	A	20001227	NO 2000-6662	20001227
BG 105143	A	20010731	BG 2001-105143	20010111

PRIORITY APPLN. INFO.: US 1998-90558P P 19980624
WO 1999-US14252 W 19990623

OTHER SOURCE(S): CASREACT 132:64065
GI

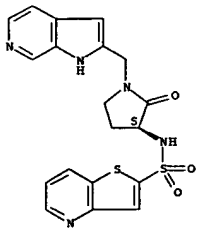


I

AB Title resins [I; R = resin; R1-R3 = H or ring system substituent (sic); R4 = F, OH, alkanoyl- or aroyloxy, SO3H, etc.; Z = Z1SO2, Z1NHSO2, Z1CH2CO, Z1Z2, etc.; Z1 = bond, (un)substituted phenylene, -alkylene, etc.; Z2 = (un)substituted phenylene] were prepared The F atom ortho to the loading site permits the absolute loading of the resin to be determined using 19F NMR.

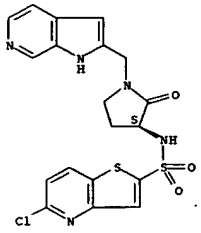
L4 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
IT **209285-84-7P 251937-98-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of fluorobenzoylated resins as solid phase synthesis supports)
RN 209285-84-7 HCAPLUS
CN Thieno[3,2-b]pyridine-2-sulfonamide, N-[(3S)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 251937-98-1 HCAPLUS
CN Thieno[3,2-b]pyridine-2-sulfonamide, 5-chloro-N-[(3S)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

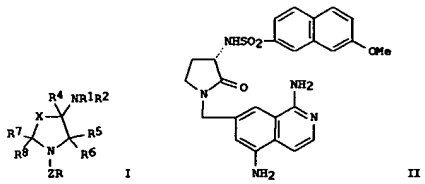
L4 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:784099 HCAPLUS
DOCUMENT NUMBER: 132:22881
TITLE: Sulfonic acid or sulfonylamino N-(heteroaralkyl)azaheterocyclic amides as inhibitors of factor Xa
INVENTOR(S): Choi-Sledeski, Yong Mi; Pauls, Heinz W.; Barton, Jeffrey N.; Ewing, William R.; Green, Daniel M.; Becker, Michael R.; Gong, Yong; Levell, Julian
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 202 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9962904	A1	19991209	WO 1999-US12312	19990603
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6602864	B1	20030805	US 1998-90492	19980603
CA 2333994	AA	19991209	CA 1999-2333994	19990603
AU 9943298	A1	19991220	AU 1999-43298	19990603
AU 758642	B2	20030327		
EP 1086099	A1	20010328	EP 1999-955266	19990603
EP 1086099	B1	20050928		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI				
BR 9910899	A	20011009	BR 1999-10899	19990603
JP 2002517393	T2	20020618	JP 2000-552115	19990603
US 6281227	B1	20010828	US 1999-453307	19991202
NO 2000005912	A	20010131	NO 2000-5912	20001122
US 2002013310	A1	20020131	US 2001-918039	20010730

PRIORITY APPLN. INFO.:
US 1998-90492 A2 19980603
US 1996-33159P P 19961213
WO 1997-US22406 A2 19971203
WO 1999-US12312 W 19990603
US 1999-453307 A3 19991202

OTHER SOURCE(S): MARPAT 132:22881
GI

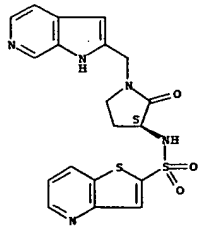
L4 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



I II

AB Aza heterocycles I [X = (CHR3)m; R = (un)substituted heteroaryl; R1, R2 = H, (un)substituted alkyl, alkenyl, aralkyl; R3 = H, OH, (un)substituted alkyl, aryl, heteroaryl; R4 = H, (un)substituted alkyl, aryl, aralkyl; R5, R6 = H; R5R6 = O; R7, R8 = H, (un)substituted alkyl, acyl, aralkyl, heteroaryl; R7R8 = O; R3R7 = alkylene; m = 0-3] were prepared I are inhibitors of the activity of Factor Xa. Thus, the amide II was prepared from 3-acetamido-4-methylbenzaldehyde, malonic acid, and 7-methoxy-2-naphthalenesulfonyl chloride in 10 steps. II had a Ki of 80 nM for inhibition of factor Xa.
IT **209285-84-7P 209285-85-8P 251937-98-1P**
251938-46-2P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of azaheterocyclic sulfonamides as inhibitors of factor Xa)
RN 209285-84-7 HCAPLUS
CN Thieno[3,2-b]pyridine-2-sulfonamide, N-[(3S)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

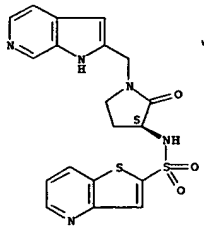


RN 209285-85-8 HCAPLUS
CN Thieno[3,2-b]pyridine-2-sulfonamide, N-[(3S)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]-, bis(trifluoroacetate) (9CI) (CA INDEX NAME)

L4 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
CM 1

CRN 209285-84-7
CMF C19 H17 N5 O3 S2

Absolute stereochemistry.



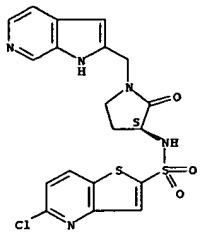
CM 2

CRN 76-05-1
CMF C2 H F3 O2

RN 251937-98-1 HCAPLUS
CN Thieno[3,2-b]pyridine-2-sulfonamide, 5-chloro-N-[(3S)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

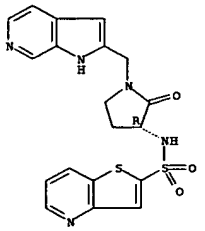


RN 251938-46-2 HCAPLUS
CN Thieno[3,2-b]pyridine-2-sulfonamide, N-[(3R)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]-, bis(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

CRN 251938-45-1
CMF C19 H17 N5 O3 S2

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

L4 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:402310 HCAPLUS
DOCUMENT NUMBER: 129:81744
TITLE: Preparation of sulfonic acid or sulfonylamino N-(heteroaralkyl)-azaheterocyclylamide compounds as inhibitors of factor Xa
INVENTOR(S): Choi-Sledeski, Yong Mi; Pauls, Henry W.; Barton, Jeffrey N.; Ewing, William R.; Green, Daniel M.; Becker, Michael R.; et al.
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 116 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

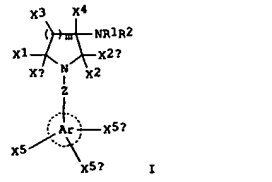
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9825611	A1	19980618	WO 1997-US22406	19971203
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2274686	AA	19980618	CA 1997-2274686	19971203
AU 9855182	A1	19980703	AU 1998-55182	19971203
AU 726637	B2	20001116		
EP 944386	A1	19990929	EP 1997-951573	19971203
EP 944386	B1	20020918		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO				
CN 1244798	A	20000216	CN 1997-181387	19971203
BR 9713921	A	20000321	BR 1997-13921	19971203
JP 2001506630	T2	20010522	JP 1998-526844	19971203
AP 1032	A	20011224	AP 1999-1552	19971203
W: GH, KE, LS, MW, SD, SZ, UG, ZW				
AT 224192	E	20021015	AT 1997-951573	19971203
PT 944386	T	20030131	PT 1997-951573	19971203
ES 2184145	T3	20030401	ES 1997-951573	19971203
ZA 9711207	A	19980720	ZA 1997-11207	19971212
US 6602864	B1	20030805	US 1998-90492	19980603
NO 9902853	A	19990810	NO 1999-2853	19990611
NO 312416	B1	20020506		
KR 2000057528	A	20000925	KR 1999-705236	19990611
US 6281227	B1	20010828	US 1999-453307	19991202
US 2002013310	A1	20020131	US 2001-918039	20010730

PRIORITY APPLN. INFO.:

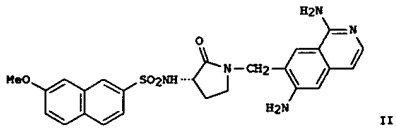
US 1996-33159P	P	19961213
WO 1997-US22406	W	19971203
US 1998-90492	A2	19980603
WO 1999-US12312	A2	19990603
US 1999-453307	A3	19991202

OTHER SOURCE(S): MARPAT 129:81744
GI

L4 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



I



II

AB The compds. of formula [I; Ar1 = a bicyclic heteroaryl containing ≥1 N atom; Z = alkenyl; R1 = H, (un)substituted alkyl, aralkyl, or heteroalkyl, hydroxyalkyl, carboxy alkyl, carbamoylalkyl, aminoalkyl, etc.; R2 = R3S(O)p, R3R4NS(O)p; R3 = (un)substituted alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroaralkyl, aralkenyl, heteroaralkenyl; or R1 and R3 taken together with N(O)p or NS(O)pNR4 through which R1 and R3 are linked from a 5 to 7 membered (un)substituted heterocyclyl; wherein p = 1, 2; R4 = (un)substituted alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, etc.; X1, X1a = H, (un)substituted alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; or X and X1a are taken together to form oxo; X3 = H, OH, (un)substituted alkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl; or X3 or one of X1 and X1a taken together form a 4 to 7 membered cycloalkyl; X5, X5a, X5b = H, (un)substituted NH2, HONH, alkoxyamino, NHNH2, (un)substituted OH, CONH2 or SO2NH2, halo, cyano, NO2, etc.; one of X5, X5a, and X5a = H, HO or (H, optionally substituted lower alkyl, hydroxy, alkoxy, or amino)NH that substitutes the distal ring of Ar1 at a position alpha to a nitrogen thereof] herein exhibit useful pharmacol. activity and accordingly are incorporated into pharmaceutical compns. and used in the treatment of patients suffering from certain medical disorders. More specifically, they are inhibitors of the activity of Factor Xa. The present invention is directed to compds. of formula I, compns. containing compds. of formula I, and their use, which are for treating
a patient suffering from, or subject to, physiol. condition (disorder) which can be ameliorated by the administration of an inhibitor of the activity of Factor Xa. The physiol. disorder is venous vasculature, arterial vasculature, abnormal thrombus formation, acute myocardial infarction, unstable angina, thromboembolism, acute vessel closure associated
with thrombolytic therapy, percutaneous transluminal coronary angioplasty, transient ischemic attacks, stroke, intermittent claudication or bypass grafting of the coronary or peripheral arteries, vessel luminal narrowing, restenosis post-coronary or venous angioplasty, maintenance of vascular

L4 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
access patency in long-term hemodialysis patients, pathol. thrombus formation occurring in the veins of the lower extremities following abdominal, knee and hip surgery, a risk of pulmonary thromboembolism, or disseminated systemic intravascular coagulopathy occurring in vascular systems during septic shock, certain viral infections and cancer. Thus, 3-(S)-amino-1-(6-amino-1-chloroisoquinolin-7-ylmethyl)pyrrolidin-2-one was coupled with 7-methoxynaphthalene-2-sulfonyl chloride followed by amination with ammonium acetate in PhOH at 115° for 2 h gave the title compd., N-[N-(isoquinolinylmethyl)oxopyrrolidinyl]naphthalenesulfonamide (II.CF3CO2H). II.CF3CO2H in vitro inhibited factor Xa, thrombin, trypsin, tissue-plasminogen activator (t-PA), plasmin and activated protein C with Ki value of 80 nM.

IT 209285-85-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of sulfonic acid or sulfonylamino N-(heteroaralkyl)-azaheterocyclylamide compds. as inhibitors of factor Xa)

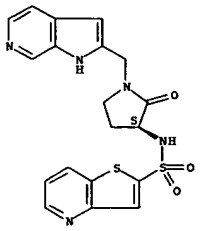
RN 209285-85-8 HCAPLUS

CN Thieno[3,2-b]pyridine-2-sulfonamide, N-[(3S)-2-oxo-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-3-pyrrolidinyl]-, bis(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

CRN 209285-84-7
CMF C19 H17 N5 O3 S2

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

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